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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/590,724	08/25/2006	Lars Burgdorf	MERCK-3229	2551

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EXAMINER	
ZAREK, PAUL E	

ART UNIT	PAPER NUMBER
1617	

NOTIFICATION DATE	DELIVERY MODE
06/03/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@mwzb.com

Office Action Summary	Application No.	Applicant(s)	
	10/590,724	BURGDORF ET AL.	
	Examiner	Art Unit	
	Paul Zarek	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,16,18,20 and 22-36* is/are pending in the application.

4a) Of the above claim(s) *11,16,18,20,22-30 and 32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,12-14,31 and 33-36* is/are rejected.

7)☒ Claim(s) *8 and 9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 1-14, 16, 18, 20, and 22-32 have been amended, Claims 33-36 have been added, and Claims 15, 17, 19, and 21 have been cancelled by the Applicant in correspondence filed on 04/14/2009. Claims 1-14, 16, 18, 20, and 22-36 are currently pending. This is the second Office Action on the merits of the claim(s). Claims 11, 16, 18, 20, 22-30, and 32 remain withdrawn as being drawn to a nonelected invention. Claims 1-10, 12-14, 31, and 33-36 read one the elected invention and are examined herein. Examiner notes that Claims 12-14 and 31 should have been examined in the Office Action mailed on 01/16/2009. Therefore, the below rejection is **non-final**.

RESPONSE TO ARGUMENTS

2. Examiner acknowledges the amendment to the specification to properly claim the benefit of international application no. PCT/EP2005/000273. The effective filing date of the instant application is 01/13/2005. The foreign priority of the instant application is 02/26/2004.

3. Examiner considered the US Patent Documents listed on the IDS submitted on 08/25/2006, as indicated by initial and arrow. Examiner notes that neither WO 02/090352 nor WO 00/27819 has been submitted by Applicants.

4. Claims 1-10 were rejected under 35 U.S.C. 112, first paragraph, for not being enabled for solvates and derivatives of formula I. This rejection is moot in light of Applicants' amendment to Claims 1-10.

5. Claims 1-8 were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds of formula I in which Ar^1 is phenyl mono- or disubstituted by R^1, Ar^2 is unsubstituted phenyl, Ar^3 is pyridinyl monosubstituted by R^1, Y is O or S, Z is CR^1R^1, R^2 is H, and R^1 may be selected from the group consisting of -H, A (as defined by Claim 1), halogen, -OH, -OA, $-CF_3$, and -CONHA, does not reasonably provide enablement for compounds of formula I in which the substituents are other than those listed above. Applicants traversed this rejection on the grounds that the Examiner has not provided evidence demonstrating or suggesting that the instant specification fails to fully enable the claims. After careful consideration, Examiner finds Applicants' arguments persuasive. The rejection of Claims 1-8 under 35 U.S.C. 112, first paragraph, for failing to be enabled for the full scope of the compounds claimed the reasons set forth in the previous Office Action is withdrawn.

6. **Below are listed new grounds of rejection that are not necessitated by amendment to the claims. Therefore, this office action is considered non-final.**

Claim Objections

7. Claims 9 and 10 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 112 (1st paragraph)

8. The text of Title 35, U.S.C. § 112, first paragraph, can be found in a prior Office action.

9. Claims 33, 35 and 36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejected claims are drawn to a compound of formula I, or a solvate (Claim 33), prodrug (Claims 33 and 36), alcoholate (Claim 35), thereof. The specification contemplates "all physiologically acceptable . . . solvates" (pg 17, lines 24-25). Alcoholates, a subgenus of solvate, are defined as "addition compounds with alcohols" (pg 23, lines 5-9).

10. Vippagunta, et al. (Advanced Drug Delivery Reviews, 2001, already of record), teach that many drugs exists in crystalline solid states in the form of solvates or hydrates (abstract, line 2). Applicants' acknowledge this (reply filed 04/14/2009, pg 15, lines 1-4). Applicants' further assert that Vippagunta, et al., demonstrates that solvates and hydrates can easily be formed by one of ordinary skill in the art (pg 15, para 7). However, Vippagunta, et al., also teach that "[t]he mere presence of water in a system is not sufficient reason to expect hydrate formation, because some compounds, though they are soluble in water, do not form hydrates" (pg 15, col 1, para 1, lines 8-11, emphasis added). Since solvates behave similarly to hydrates (Vippagunta, et al., pg 15, col 1, para 1, lines 18-19), one of ordinary skill in the art could not reasonably predict which solvent would produce a solvate. Indeed, Vippagunta, et al., state that predicting the formation of solvates or hydrates of a compound is "complex and difficult." "There may be too many possibilities so that no computer programs are currently available for predicting the crystal structures of hydrates and solvates" (pg 18, Section 3.4). As a subgenus, alcoholate is exceedingly broad covering every compound comprising an –OH. This ranges from methanol to

glycerol to nonadecanol, and beyond. The instant specification provides no working examples of a solvate or hydrate of a compound of formula I. The instant specification specifically contemplates hydrate, methanolate and ethanolate.

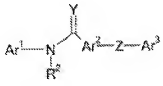
11. The specification exemplifies, but does not define, "prodrug compounds" as "compounds of formula I which have been modified with, for example, alkyl or acyl groups, sugars or oligopeptides and which are rapidly cleaved or liberated in the organism to give effective compounds according to the invention (pg 22, lines 23-26). Prodrugs of formula I, then, are any compounds that are cleaved *in vivo* to generate formula I. It cannot be known *a priori* whether a given molecule will be an effective prodrug. Van de Waterbeemd, et al., teach that experimental data is necessary to determine whether a given molecule would be an effective prodrug (pg 1328, para 3).

12. Given the inherent unpredictability of which solvent would generate a solvate of formula I, which derivative would be a prodrug of formula I, and the dearth of working examples, one of ordinary skill in the art would have reasonably concluded that Applicants were not in possession of the claimed invention at the time of filing.

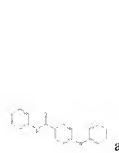
13. Claims 1-8, 12-14, and 33-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds of formula I in which Ar^1 is phenyl mono- or disubstituted by R^1, Ar^2 is unsubstituted phenyl, Ar^3 is pyridinyl monosubstituted by R^1, Y is O or S, Z is CR^1R^1, R^2 is H, and R^1 may be selected from the group consisting of -H, A (as defined by Claim 1), halogen, -OH, -OA, $-CF_3$, and -CONHA, does not reasonably provide enablement for compounds of formula I in which the substituents are other than those listed above. The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The Wands factors are discussed below:

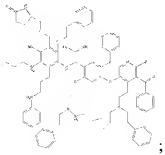
a. *The breadth of the claim*: The rejected claims are drawn to a compound of



formula I, , a pharmaceutical composition, thereof, or a kit comprising formula I. Two examples of compounds encompassed by formula I are:



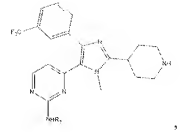
and,



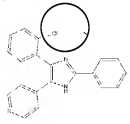
;

b. *Nature of the invention*: The nature of the invention is compounds of formula I. Applicants disclose that the compounds of formula I are kinase inhibitors, particularly tyrosine and Raf kinase inhibitors (pg 3, lines 9-10)

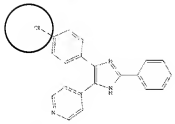
c. *The state of the prior art*: The compounds of the elected group of formula I are novel over the prior art. Liverton, et al., teach p38 and c-Raf kinase inhibitors that are structurally unrelated to the claimed compounds. Liverton, et al., teach that minor changes in the chemical structure significantly affect the inhibitory capacity of the



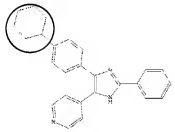
resultant molecules. For example, compound of the formula, , when R_1 is (R)-PhCH(CH_3) (cmpd 41) gives 48% inhibition of c-Raf at 5 μM, which the stereoisomer wherein R_1 is (S)-PhCH(CH_3) (cmpd 39) does not inhibit c-Raf (Table 4). Liverton also demonstrate that minor differences (see circles) greatly impact inhibition of c-Raf:



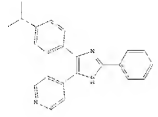
- (cmpd 3c) IC_{50} 610 nM



- (cmpd 3e) IC_{50} 56 nM



- (cmpd 3p) IC_{50} 570 nM



- (cmpd 3q) IC_{50} >10,000 (Table 2)

d. *Level of one of ordinary skill in the art*:Medicinal chemists would represent one of ordinary skill in the art. Consequently, the level of ordinary skill would be high;

e. *Level of predictability in the art*: The pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher* (427 F. 2d 833, 166USPQ 18 (CCPA 1970)) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Liverton, et al., demonstrate that relatively minor changes (i.e. positional isomers or changing the alkyl subgroup) to an inhibitor of c-Raf dramatically affects the ability of the resulting compound to inhibit c-Raf.;

f. *Amount of direction provided by the inventor*: Applicant disclose that the claimed compounds are inhibitors of Raf kinase;

g. *Existence of working examples*: All of the disclosed embodiments fall within particularly preferred embodiments (pg 19, lines 23-31), to which this scope of enablement applies. Applicant has tested only the 29 disclosed compounds and states that these compounds inhibit VEGF-stimulated mitogenesis of human umbilical vascular endothelial cells TIE-2 kinase phosphorylation (Example 3, Methods 3 and 5). It is noted that Applicant did not show the results of these experiments; and,

h. *Quantity or experimentation needed to make or use the invention based on the content of the disclosure*: Applicant has made and tested only a very small subset of the possible compounds encompassed by the rejected claims. The instant specification does not provide sufficient guidance to enable one of ordinary skill in the art at the time the invention was made to make all of the huge number of compounds claimed. Indeed, the compounds that are encompassed by the instant claims are exceedingly diverse and would not be considered obvious variants of each other. Moreover, given the specific binding requirements for c-Raf inhibition disclosed by Liverton, et al., one of ordinary skill in the art would not reasonably expect that a substantial subset of such a divergent set of compounds would be c-Raf inhibitors.

Although working examples are not required for the satisfaction of the enablement requirement, the presence or absence of such examples is a factor which Examiner must consider. The demonstration by Liverton, et al., that small alterations to an inhibitor of c-Raf renders the resultant compound unable to inhibit c-Raf (compare compounds 3e and 3q) indicates that merely have the same generic core is not sufficient to inhibit c-Raf.

"A patent is not a hunting license. It is not a reward for search but compensation for its successful conclusion and patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable." (*Genentech Inc v Nova Nordisk* 42 USPQ 2d 1001) One of ordinary skill could not reasonably determine which of the claimed compounds would be effective Raf kinase inhibitors. The instant specification does not enable one of ordinary skill in the art

to make and use the invention commensurate with the scope of the rejected claims.

Undue and unpredictable experimentation would be required.

Claim Rejections - 35 USC § 112 (2nd paragraph)

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 14 recites the limitation of an "additional pharmaceutically active ingredient." Neither the specification nor the claims define what is meant by an "additional pharmaceutically active ingredient." Thus, the metes and bounds of this claim are unknown and the claim is considered indefinite.

16. Claim 36 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 36 recites the limitation that a compound of formula I "has been modified with an alkyl or acyl group, or with a sugar or oligopeptide." Neither the specification nor the claims define what is meant by "modified." Thus, the metes and bounds of this claim are unknown and the claim is considered indefinite.

Conclusion

17. Claims 1-8, 12-14, and 33-36 are rejected. Claims 9 and 10 are objected to.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul Zarek whose telephone number is (571) 270-5754. The examiner can normally be reached on Monday-Thursday, 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

PEZ

/San-ming Hui/
Primary Examiner, Art Unit 1617